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10/580,248	07/20/2006	Mimi Adachi	64517.000003	6084

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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,248	ADACHI ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *3,13,14,26-30,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12,15-25 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-33 are under pending.

Election/Restrictions

Applicant's election with traverse of Group I claims 1-2, 4-12, 15-25, 31 in the reply filed on 2/25/07 is acknowledged. The traversal is on the ground(s) that the special technical feature of claim 1 comprises (a) cyclin, (b) cyclin-dependent kinase, and (c) one or plurality of a gene encoding a factor that inhibit the production, function or action of Cip/kip family protein or a nucleic acid that inhibits the production of Cip/kip family protein. Applicants argue this special technical feature is shared by each of Groups I, II, III, IV, V, and VI. Indeed, Groups I, II, III, and IV are drawn to a method for proliferating cardiomyocytes comprising a step of introducing (a) cyclin, (b) cyclin-dependent kinase, and (c) one or a plurality of a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein, or a nucleic acid that inhibits the production of Cip/Kip family protein, into cardiomyocytes either using a factor which is an encoding protein factor in vivo or in vitro or using a nucleic acid that is siRNA specific to a gene encoding the Cip/Kip family protein in vivo or in vitro. Furthermore, Groups V and VI are drawn to vectors that comprise (a) cyclin gene, (b) cyclin-dependent kinase gene, and (c) one or a plurality of a gene encoding a factor that inhibit the production, function or action of Cip/Kip family protein, or a nucleic acid that inhibits the production of Cip/Kip family protein. Accordingly, Groups I, II, III, IV, V, and VI share the same special technical feature. This is not found persuasive because the unity of invention between the Groups does not exist. Such is not persuasive as, the method of Group I requires the special technical feature of (a) cyclin, (b) cyclin-dependent kinase, and (c) one or plurality of a gene encoding a factor that inhibit the

production, function or action of Cip/kip family protein or a nucleic acid that inhibits the production of Cip/kip family protein. However, the method of Group I does not require a nucleic acid that inhibits the production of Cip/kip family proteins is siRNA specific to a gene encoding the Cip/kip family protein which is required for Group II. As such Groups I and II do not share the same special technical feature and thus according to PCT lack of unity guidelines, under 35 USC 372 restriction practice, when the unity of Groups I and II is fallen then all the Groups are fallen apart due to the lack of a special technical feature. The basis of the lack of unity is not based on the use of cyclin and a cyclin dependent kinase but the structure "the" gene encoding a factor that inhibit the production, function or action of Cip/kip and the cite of the method. The differences in structure of the genes and location of the method indicates a lack of common technical feature. 37 CFR 1.475 does not permit examination of multiple methods and products where there is no common technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3, 13-14, 26-30, 32-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/15/07

Claims 1-2, 4-12, 15-25, 31 are under consideration.

Claim Objections

Claims 1, 4-12, 15, 16 are objected to because of the following informalities: The claims encompass a method for proliferating cardiomyocytes in vivo which is to the non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-2, 4-8, 15-21 and 31** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tamamori-Adachi et al,** (Circ Res, 92:e12-e19, 2003) in view of **Poolman et al,** (Circ Res, 85: 117-127, 1999).

Tamamori-Adachi teaches a method for proliferating cardiomyocytes in vitro comprising of co-introducing a cyclin and a cyclin dependent kinase using an adenovirus containing cyclin D1 which directly linked to nuclear localization signal to target the cyclin into the nucleus and an adenovirus containing the cyclin-dependent kinase CDK4 (p 2, 1st column under materials and methods and abstract). Tamamori-Adachi teaches that when these viruses are injected in adult rat hearts, they have shown that postmitotic cardiomyocytes have the potential to proliferate provided the complex cyclin D1/CDK4 accumulates in the nucleus and the prevention of their nuclear import plays a critical role as a physical barrier to prevent cardiomyocyte proliferation (abstract and p 2 under in vivo study). The precise mechanism preventing cyclin D1 nuclear accumulation remains unclear (Tamamori-Adachi, p 7, 1st column, 3rd paragraph). D-type cyclins and CDK4 lack a consensus nuclear localization signals (NLSs) and $p21^{cip1}$ and $p27^{kip1}$, which contain NLSs promote the assembly and nuclear localization of the cyclinD1/CDK4 complex (Tamamori-Adachi, p 7, 1st column, 3rd paragraph). Tamamori-Adachi also teaches that in postmitotic cardiomyocytes they have shown that the cyclin D1/CDK4 complex was formed but remained in the cytoplasm (figure 2D). In addition, the cytoplasmic cyclin D1/CDK4 complex

associated with $p21^{cip1}$ or $p27^{kip1}$, did not promote nuclear localization of cyclin D1/CDK4 complex (Tamamori-Adachi, p 7, 1st column, 3rd paragraph). Tamamori-Adachi suggests that investigation of mechanisms preventing cyclin D1 nuclear import in cardiomyocytes will provide findings important for the development of regenerating cardiomyocytes for therapeutic applications (p 8, 1st column, 1st paragraph). Tamamori-Adachi differs from the claimed invention by not teaching the introduction of a gene encoding a factor that inhibits the production or function of Cip/kip family proteins into cardiomyocyte cultures.

However, at the time of the instant invention, **Poolman** teaches that loss of CDK1 molecule $p27^{kip1}$ in the mouse heart results in a prolonged proliferation of cardiac myocytes and a perturbation of cardiac myocyte hypertrophy and differentiation (p 126, 2nd column, 2nd paragraph). As such, Poolman et al provide sufficient motivation for one of ordinary skill in the art to introduce a gene encoding a factor that inhibits the production or function of $p27^{kip1}$ to the cadiomyocyte system of **Tamamori-Adachi** in order to promote the nuclear localization of the cytoplasmic cyclin D1/CDK4 complex and promote cardiomyocyte proliferation.

Accordingly, in view of the teachings of **Poolman et al,** it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the cardiomyocyte cell culture system of **Tamamori-Adachi** by use of a gene encoding for factor to inhibit the production of the $p27^{kip1}$ gene in cultured cardiomyocytes with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification because **Tamamori-Adachi** suggests that investigation of mechanisms preventing cyclin D1 nuclear import in postmitotic cardiomyocytes will provide findings important for the development of regenerating cardiomyocytes for therapeutic applications.

Claims **9-12, 22-25** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tamamori-Adachi et al,** (Circ Res, 92:e12-e19, 2003) in view of **Poolman et al,** (Circ Res, 85: 117-127, 1999) as applied to claims **1-2, 4-8, 15-21 and 31** above, and further in view of **Tsvetkov et al,** (Current Biology, 9: 661-664, 1999); **Yu et al,** (PNAS, 95: 11324-11329, 1998).

The teachings of the **Tamamori-Adachi et al,** (Circ Res, 92:e12-e19, 2003) and **Poolman et al,** (Circ Res, 85: 117-127, 1999) are outlined above.

Neither **Tamamori-Adachi et al** or **Poolman et al,** teach a factor that inhibits the production or function or action of Cip/kip family proteins with an action to promote the degradation of the Cip/kip family protein.

However, at the time the claimed invention was made, **Tsvetkov et al,** (Current Biology, 9: 661-664, 1999) teaches $\underline{p27^{kip1}}$, ubiquitination and degradation is required by the SCF^{skp2} complex (p 661, 2nd column and throughout the whole document). **Tsvetkov** teaches that SCF^{skp2} specifically binds to the Thr187-phosphoryalted form of p27 and targets it for degradation through the ubiquitin-dependent process (p 663, 1st column, last paragraph).

Accordingly, in view of the teaching of Tamamori that prevention of nuclear import of CyD1/CD4 prevents cardiomyocyte proliferation and in view of the teachings of Poolman that loss of $\underline{p27^{kip1}}$, promotes cardiomyocyte proliferation it would have been *prima facia* obvious to introduce a gene encoding for the degradation of $\underline{p27^{kip1}}$ as taught by **Tsvetkov** into the Tamamori-Adachi system with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification because Tamamori-Adachi teaches that in postmitotic cardiomyocytes the cyclin D1/CDK4 complex was formed but remained in the cytoplasm and the cytoplasmic cyclin D1/CDK4 complex associated with $\underline{p27^{kip1}}$, did not promote nuclear localization of cyclin D1/CDK4 complex.

At the time of the instant invention, **Yu et al,** (PNAS, 95: 11324-11329, 1998) teaches an expression vector encoding $p19^{skp1}$ or $p45^{skp2}$ (p 11325, 1st column, 2nd paragraph under plasmids, chemicals and antibodies). Based on the teachings of Tamamori-Adachi and the high level of skill in the art of molecular cloning the skilled artisan would have had a reasonable expectation of success in generating proliferating cardiomyocytes by using a gene encoding for $p45^{skp2}$ that inhibits production of $p27^{kip1}$, by ubiqutiantion thus, promoting the nuclear localization of the CD1/CDK4 complex .

Thus, the claimed invention as a whole is clearly prima facie obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4-7, 16-21, 31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4, 18-19 of U.S. Patent No. 10/713,008. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass a method for proliferating cardiomyocytes comprising introducing a cyclin and a cyclin dependent kinase and introducing

genes into cardiomyocytes. For example, claims 1-2 of instant application encompass a method for proliferating cardiomyocytes by introducing a cyclin, a cyclin dependent kinase and one or a plurality of a gene encoding a factor that inhibits the production, function of Cip/kip family protein and culturing the cardiomyocytes in vitro. Dependent claims limit the cyclin, wherein cyclin is a capable of activating CDK4 or CDK6. Dependent claims also limit the cyclin dependent kinase, wherein cyclin dependent kinase is a cyclin to be activated by cyclin D. Whereas, claim 1 of the application 10/713,008 is directed to a method for proliferating cardiomyocytes comprising introducing a D-type cyclin and a cyclin dependent kinase into the nucleus of cardiomyocytes and cultivating or holding said cells wherein said cycllin dependent kinase id CDK4 or CDK6. Thus, the claims of the instant application differs from the application 10/713,008 only with respect o broader scope of genes that could be used in the method for proliferating cardiomyocytes in culture.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 11, 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims cite the phrase "capable". It is not clear what are the metes and bound of cyclin being capable of activating CDK4 of CDK6.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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Art Unit 1632

Deborah Crouch

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